REMARKS

Claims 1, 3, 4 and 6-10 are pending in the instant application. Claim 1, 3, 4, and 6-10 have been rejected. Reconsideration is respectfully requested in light of the following remarks.

Rejection of Claims 1, 3, 4 and 6-10 under 35 U.S.C. 103(a)

The rejection of claims 1, 3, 4 and 6-10 under 35 U.S.C. 103(a) as being unpatentable over Mao et al. (U.S. Patent 6,166,173) has been maintained.

Applicants respectfully traverse this rejection.

Arguments presented by Applicants in the previous response were deemed unpersuasive. In particular, in response to Applicants' argument that Mao discloses a string list of potential drugs without providing data to show the stability and/or release and/or undesirable effects for any of the exemplary antipsychotic drugs, the Examiner suggests "that when considering antipsychotic drugs, the list is quite limited to clozapine, haloperidol or risperidone and any of them including haloperidol can be incorporated in the implant". Further, with respect to teachings in the specification regarding thiothixene implants having decreased stability, the Examiner suggests that "clozapine, haloperidol or risperidone was not mentioned as ones who stability decreases with increasing concentration".

Accordingly, in an earnest effort to advance the prosecution of this caser, Applicants are submitting herewith a Declaration by inventor, Dr. Steven Siegel, outlining experiments conducted with clozapine implants.

As discussed in paragraph 4 of Dr. Siegel's Declaration, clozapine implants were designed initially with a goal of releasing active drug (clozapine) for 30 days using 50:50 PLGA with 20% drug load. The same polymer composition, design, fabrication methods and drug loads resulted in a haloperidol implant with 30 day release of haloperidol (see paragraph 4 of Dr. Siegel's Declaration).

However, problems arose during fabrication of the clozapine implant.

In particular, as discussed in paragraph 5 of Dr. Siegel's Declaration, clozapine is not soluble in the same solvents as PLGA. Therefore, unlike step (a) of claim 4 of the instant application, which states that haloperidol and a biodegradable polymer were dissolved in acetone, composite solvents containing both ethanol and acetone were required to form a solution containing PLGA and clozapine (see paragraph 5 of Dr. Siegel's Declaration). As discussed in paragraph 5 of Dr. Siegel's Declaration, differing solubility as the composition of the mixed solvent changes during the evaporation process (i.e. ethanol and acetone components will evaporate at different rates) is expected to

cause unequal precipitation of the clozapine and PLGA in the implant.

In addition, Dr. Siegel described the clozapine implants as soft and gooey at processing temperatures and conditions needed to mold PLGA (see paragraph 6 of Dr. Siegel's Declaration). Accordingly, unlike the haloperidol implants which were hard and did not stick to molds or deform during production, with clozapine they were unable to form fully dense implants. Instead, the "soft and gooey" clozapine implants adhered to the Teflon coated molds and deforms during removal (see paragraph 6 of Dr. Siegel's Declaration).

Finally, and most importantly, in vitro and in vivo experiments with the clozapine implants indicated that these implants were not capable of delivering steady state concentrations of clozapine or delivering clozapine for extended periods of 5 months or more in accordance with the claims of the instant application. Paragraph 7 of Dr. Siegel's Declaration describes in vitro experiments with the clozapine implants. As shown in the Figure provided with Dr. Siegel's Declaration, clozapine implants were only capable of releasing drug for 18 days (arrow), which was approximately 60% of the interval achieved for haloperidol using the same approach. Further, as discussed in detail in Paragraph 8 of Dr. Siegel's Declaration and shown in the

table provided therewith, in vivo experiments with clozapine implants revealed highly variable release with inconsistent serum levels of clozapine with implants prepared via a similar method to the haloperidol implants. These results differed significantly from Dr. Siegel's experience with haloperidol implants, which yield highly consistent release and serum levels in vivo (see paragraph 8 of Dr. Siegel's Declaration).

As demonstrated by data presented in Dr. Siegel's Declaration, the methods used to produce the haloperidol implants of the present invention were not generalizable to production of a clozapine implant with characteristics similar to the instant claimed invention.

Accordingly, the disclosure of Mao, with its string list of potential drugs, even when limited to the antipsychotic drugs clozapine, haloperidol or risperidone, and its absence of any data whatsoever regarding stability and/or release for any of the listed exemplary antipsychotic agents, clearly fails to provide the requisite reasonable expectation of success with respect to the instant claimed invention.

Accordingly, the Mao reference fails to meet the basic criteria required to establish a prima facie case of obviousness with respect to the instant invention.

Further, MPEP 2144.09 and the case law are clear; a prima facie case of obviousness is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. In re Papesch, 315 F.2d 381, 137 (USPQ 43 (CCPA 1963). Data presented in Dr. Siegel's Declaration is demonstrative of the superior unexpected properties of the claimed haloperidol implant over implants with other antipsychotic agents such as clozapine. Such data clearly rebuts any prima facie case of obviousness which may or may not have been made over the general teachings of Mao et al. with its string list of potential drugs, even when limited to the antipsychotic drugs clozapine, haloperidol or risperidone, and its absence of any data whatsoever regarding stability and/or release for any of the listed exemplary antipsychotic agents.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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